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A Biomimetic Strategy for the Synthesis of the Tricyclic Dibenzofuran-1,4-dione Core of Popolohuanone E

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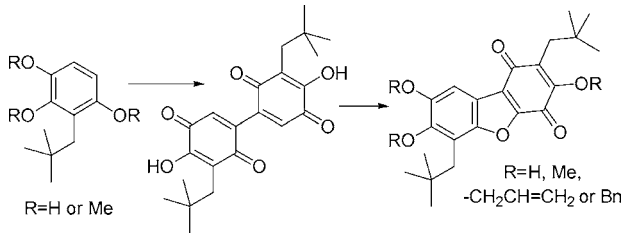
ABSTRACT



A concise synthesis of the complete tricyclic dibenzofuran-1,4-dione aromatic core of popolohuanone E has been demonstrated by mild base treatment of a biquinone intermediate, thus establishing a biomimetic route to this family of heterocyclic ring systems and the total synthesis of popolohuanone E.

Popolohuanone E (**1**), which contains a novel hydroxylated dibenzofuran-1,4-dione core as its central structural element, was isolated from the marine sponge *Dysdiea* sp. in 1990.[1] The biological activity of **1** has been shown to include the inhibition of topoisomerase II (IC_{50} = 400 nM) and selective cytotoxicity against the A549 nonsmall human lung cancer cell line (2.5 μg/mL), which is particularly resistant to medical treatment.[1] In addition, **1** is not appreciably cytotoxic (>20 μg/mL) to CV-1 nontumor monkey kidney cells.

The combination of structural complexity and promising biological activity exhibited by **1** has stimulated the development of methodology for the preparation of dibenzofuran-1,4-diones and the total synthesis of the related metabolite areranol **2** (Figure 1), itself isolated from *Dysdiea* sp. among other marine sources.[1,2] Katoh et al. have reported the total synthesis of (+)-areranol **2**, in addition to the synthesis of model compounds related to the core of popolohuanone E.[3,4]

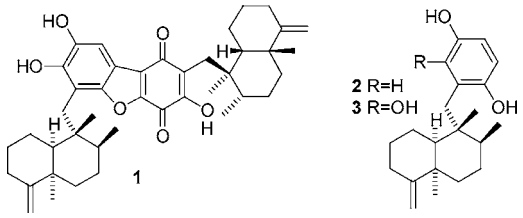


Figure 1.

We, along with others,[5] have achieved a formal total synthesis of racemic **2** and have developed a method for regioselective dibenzofuran-1,4-dione synthesis.[6,7] No total syn-

[†] Corresponding author for X-ray crystal structures.

(1) Carney, J. R.; Scheuer, P. J. *Tetrahedron Lett.* **1993**, *34*, 3727. *Popolohua* means *purplish blue as the sea* in Hawaiian.

(2) Areranol (**2**) was first isolated from *Dysidea arenaria* in 1984 and subsequently from a *Fenestraspongia* species; see: (a) Schmitz, F. J.; Lakshmi, V.; Powell, D. R.; van der Helm, D. *J. Org. Chem.* **1984**, *49*, 241. (b) Carte, B.; Rose, C. B.; Faulkner, D. J. *J. Org. Chem.* **1985**, *50*, 2785.

(3) Kawano, H.; Itoh, M.; Katoh, T.; Terashima, S. *Tetrahedron Lett.* **1997**, *38*, 7769.

(4) Ueki, Y.; Itoh, M.; Katoh, T.; Terashima, S. *Tetrahedron Lett.* **1996**, *37*, 5719.

(5) Watson, A. T.; Park, K.; Wiemer, D. F.; Scott, W. *J. Org. Chem.* **1995**, *60*, 5102.

(6) Anderson, J. C.; Pearson, D. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2023.

(7) Anderson, J. C.; Denton, R. M.; Hickin, G. H.; Wilson, C. *Tetrahedron* **2004**, *60*, 2327.

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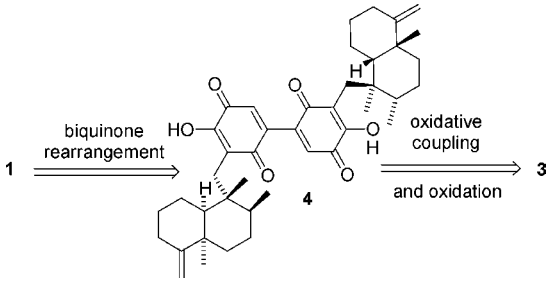
thesis of **1** has been accomplished to date; however, Katoh et al. very nearly achieved this goal in preparing 8-*O*-methylpopolohuanone E in 2001.[8]

It has been proposed that **1** may be derived from the as yet unreported 6′-hydroxyareranol **3** (Figure 1).[1,9] Upon this basis, we reasoned that **3** could undergo oxidative phenolic coupling[10] and oxidation giving rise to the C_2-symmetric biquinone **4** which we expected would undergo rearrangement to **1** (Scheme 1).[11] We recognized the potential

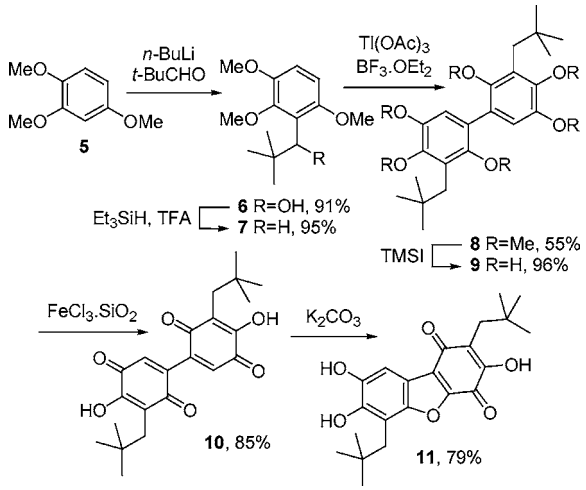
Scheme 1. Possible Biomimetic Retrosynthesis[1]



efficiency of this approach since it exploits the latent C_2 symmetry contained in the natural product. Related to this approach, Benbow et al. have investigated an intramolecular phenol quinone cyclization in an attempt to prepare the tricyclic core of **1**.[12] This unsuccessful investigation uncovered a complex series of redox processes and strengthened our belief that **1** is formed from the rearrangement of a biquinone species rather than a simple intramolecular cyclization between a phenol and a quinone. The recent application of a similar biquinone rearrangement reaction in the synthesis of violet-quinone by the Takeya group[13] prompts us to report our results on the biomimetic synthesis of the dibenzofuran-1,4-dione core of **1**.

We began our investigation by attempting to mimic the biomimetic hypothesis outlined in Scheme 1 in a stepwise fashion (Scheme 2). Lithiation of **5** followed by addition to pivaldehyde and deoxygenation of the resultant benzylic hydroxyl gave rise to **7** in excellent yield.[6] Oxidative coupling[14] afforded biaryl **8**, whose structure was confirmed by X-ray analysis.[6] Global demethylation followed by

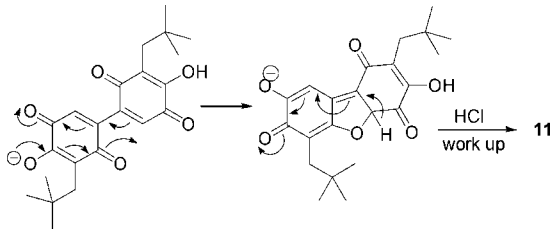
Scheme 2. Biomimetic Synthesis of Popolohuanone E Core



oxidation of the sensitive hexaol afforded biquinone **10** in high yield. The key biomimetic biquinone rearrangement was accomplished under very mild conditions[15] affording the complete tricyclic aromatic core of popolohuanone E in good yield as a dark purple solid. The substitution pattern of **11** was assigned by comparison of ^{13}C NMR data with that of Katoh,[16] which in turn relied upon data from the original spectral structure determination of **1** by Carrey and Scheuer.[1] Our assignments, and ultimately that of the original structure determination, were later confirmed by single-crystal X-ray structure determination of the tri-*O*-Me analogue (vide infra).

A reasonable mechanism for the biquinone rearrangement (Scheme 3) involves reversible conjugate addition of one

Scheme 3. Mechanism of Biquinone Rearrangement



quinone ring to the other. From our experiments it would seem that our base-promoted cyclization is faster than a similar reported acid-catalyzed process.[11c] Tautomerization and eventual protonation upon workup enable the isolation of the dibenzofuran-1,4-dione.

(8) Katoh, T.; Nakatani, M.; Shikita, S.; Sampe, R.; Ishiwata, A.; Ohmori, O.; Nakamura, M.; Terashima, S. *Org. Lett.* **2001**, *3*, 2701.

(9) Whilst 6′-hydroxyareranol has not been isolated the related compound 6′-hydroxyavarol the $\Delta^{3,4}$ isomer and C-5 epimer has been isolated from *Dysidea cinerea*; see: Hirsh, S.; Rudi, A.; Kashman, Y.; Loya, Y. *J. Nat. Prod.* **1991**, *54*, 92.

(10) For reviews, see (a) Taylor, W. I.; Battersby, A. R. *Oxidative Coupling of Phenols*; Marcel Dekker: New York, 1967. (b) Sainsbury, M. *Tetrahedron* **1980**, *36*, 3327. (c) Bringmann, G.; Walter, R.; Weirich, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *29*, 977.

(11) (a) Erdtman, H. G. H. *Proc. R. Soc.* **1934**, *143*, 233. (b) Pummerer, R.; Stein, B.; Riegelbauer, G.; Rosenhauer, E. *Ber. Dtsch. Chem. Ges.* **1939**, *72*, 623. (c) Shand, A. J.; Thomspon, R. H. *Tetrahedron* **1963**, *19*, 1919. (d) Bernais-Barbry, S.; Bonneau, R.; Castellan, A. *J. Phys. Chem. A* **1999**, *103*, 11136.

(12) (a) Benbow, J. W.; Martinez, B. L.; Anderson, W. L. *J. Org. Chem.* **1997**, *62*, 9345. (b) Benbow, J. W.; Katoch-Rouse, R. *J. Org. Chem.* **2001**, *66*, 4965.

(13) Ogata, T.; Okamoto, I.; Kotani, E.; Takeya, T. *Tetrahedron* **2004**, *60*, 3941.

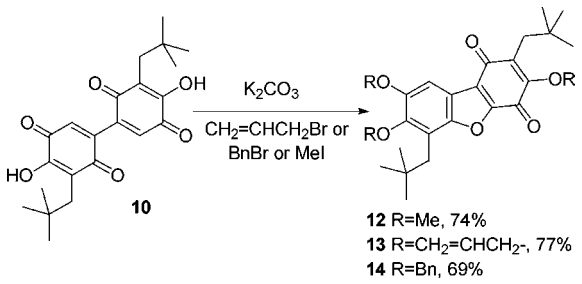
(14) McKillop, A.; Turrel, A. G.; Young, D. W.; Taylor, E. C. *J. Am. Chem. Soc.* **1980**, *102*, 6504.

(15) Conditions used to effect similar rearrangement reactions involve acidic conditions and elevated temperatures or the use of powerful UV lamps, which would not be suitable for our total synthesis studies. See refs 10a−c and 13.

(16) A similar compound possessing Me groups instead of neopentyl substituents was made by Katoh (ref 4). We are very grateful to Professor Katoh for sending us the relevant NMR spectra from ref 4, which made our initial NMR assignment possible.

With the biomimetic rearrangement reaction in hand we next examined the possibility of rearrangement and in situ hydroxyl protection. Protected forms of the dibenzofuran-1,4-dione core were of interest from the point of view of our total synthesis of **1**. We were mindful of Katoh's very near synthesis of **1**[8] and their finding that late stage 8-*O*-Me deprotection was impossible. Accordingly, we wished to identify hydroxyl protecting groups that could be cleaved under very mild conditions. Addition of a suitable electrophilic species to the base-induced biquinone rearrangement reaction gave rise to protected dibenzofuran-1,4-diones in good yield (Scheme 4) as dark red crystalline solids. The

Scheme 4. Rearrangement and in Situ Protetcion



structure of the trimethyl-protected dibenzofuran-1,4-dione **12** was confirmed by single-crystal X-ray determination[17] and supported our assignments of **11**, **13,** and **14** by ^{13}C NMR, along with previous assignments by other workers in the field.[1,8]

The deprotection of the allyl- and benzyl-protected dibenzofuran-1,4-diones was next investigated. Exposure of **13** to $Pd(PPh_3)_4$ in MeOH with K_2CO_3[18] led to the monomethyl ether **15** in excellent yield.[19] Subsequent treatment with *n*-butylthiolate[20] afforded the fully deprotected core **11** in a two-step yield of 80%. More concisely though, global debenzylation of **14** was achieved in a straightforward manner giving **11** in 95% yield. No reduction of the quinone ring was observed. In our opinion, both of these protection/deprotection protocols should be applicable in our total synthesis of **1**.

Finally, we wished to study a more direct biomimetic synthesis which would involve the coupling of two unprotected aryl units. Thus, a model **16** of 6′-hydroxyareranol (**3**), the proposed biogenetic precursor of **1**, was prepared

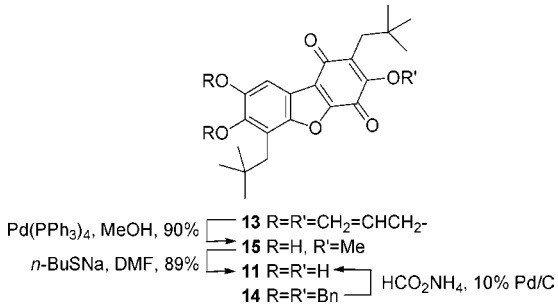
(17) Crystallographic data (excluding structure factors) for **12** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 253583. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

(18) Vutukuri, D. R.; Bharathi, P.; Yu, Z.; Rajasekaran, K.; Tran, M.; Thayumanavan, S. *J. Org. Chem.* **2002**, *68*, 1146.

(19) Various other solvents and nucleophiles were screened in this reaction in an attempt to produce the fully deallylated product; however, all resulted in the formation of multiple unwanted products and only trace (<5% by ^1H NMR) amounts of fully deallylated product.

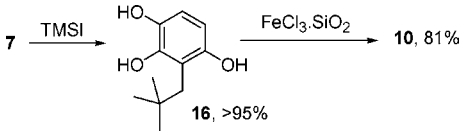
(20) Bartlett, P. A.; Johnson, W. S. *Tetrahedron Lett.* **1970**, 4459.

Scheme 5. Deprotection of Popolohuanone-Like Core



(Scheme 5). The model triol **16**, formed from the demethylation of **7** with TMSI, proved to be considerably more reactive than its protected counterpart **7**. Dimerization was best achieved using a very mild oxidant which through optimization was determined to be silica supported $FeCl_3$. In a single operation from **16**, aryl−aryl bond construction was followed by oxidation to biquinone **10**, the cyclization precursor to the tricyclic aromatic core of popolohuanone E (Scheme 6) in 81% yield.

Scheme 6. Direct Biomimetic Synthesis



We have demonstrated a biomimetic synthesis of the hydroxylated dibenofuran-1,4-dione core of popolohuanone E (**1**) and have confirmed spectral assignments of this class of heterocyclic system by single-crystal X-ray structure determination. The key rearrangement reaction takes place from a biquinone system under mild reaction conditions and should also be applicable to the synthesis of simpler congeners of this heterocyclic system. Rearrangement with in situ protection, and subsequent removal of *O*-allyl and *O*-benzyl protecting groups, has demonstrated that this biomimetic approach is a viable end-game strategy for the total synthesis of **1** which is currently underway.

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Supporting Information Available: Experimental procedures, characterization data, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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